Message

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Subject: EPA IRIS Public Science Meeting - May 10th 2016 documents and information
Attachments: RDX_IRIS_TOXICOLOGICAL_REVIEW__SUPPINF_PCD.PDF; RDX_IRIS_TOXICOLOGICAL_REVIEW_PCD.PDF

Hi Dr. Ehrich –

As I promised this morning, attached are the two sections of the IRIS Toxicological Review of RDX – which is the document that we will be discussing at the meeting next week. The file named *RDX_IRIS_Toxicological_Review_PCD.PDF* is the main document. The other file *RDX_IRIS_TOXICOLOGICAL_REVIEW_SUPPINF_PCD.PDF* is called the "supplementary information" document and contains the appendices. A complete description of the meeting and a link to the documents is available on the meeting website: https://www.epa.gov/iris/iris-public-science-meeting-may-2016.

In advance of the Public Science Meeting, the IRIS Program identified "science topics" related to the RDX assessment and NAS assisted with requesting experts to help evaluate the responses to these. The science topics are available on the meeting website, but I have pasted some of the text below. You were identified by NAS to discuss the 3rd science topic (I included the description of this one but the entirety for all three is on the website).

Key Science Topics:

Science Topic 1: Suppurative prostatitis as a marker for hazard to the urogenital system following RDX exposure.

Science Topic 2: Evaluation and use of RDX PBPK models.

Science Topic 3: Neurotoxicity observed with RDX – including consideration of dose and duration of exposure and the potential relationship to mortality.

In the majority of studies, RDX exposure was associated with convulsions. Characterization of the relationship between mortality and convulsions was based on several studies that reported observing convulsions before unscheduled deaths (Crouse et al., 2006; Angerhofer et al., 1986; Levine et al.,1983b Cholakis et al., 1980). In addition, treatment-related mortality was observed in several studies at doses as low as those associated with nervous system effects (Crouse et al., 2006, Angerhofer et al., 1986; Levine et al., 1983b; Levine et al., 1981; Cholakis et al., 1980; Von Oettingen et al., 1949). The 90-day study by Crouse et al. (2006) provided the most detailed information on the relationship between convulsions and mortality. However, additional individual animal data from this study (Johnson, 2015) did not show a clear correspondence between convulsions and mortality (e.g., not all animals that convulsed died during the study).

Because some studies identified mortality at the same dose of RDX that induced nervous system effects, additional analysis of the mortality data was undertaken. This analysis involved comparison of dose-response relationships for mortality in rodents exposed to RDX for durations up to 90 days with dose-response relationships for convulsions following similar exposure durations. Specifically, LD_{01} values (the dose expected

to be lethal to 1% of the animals) derived using mortality data sets were compared to benchmark dose (BMD_{01}) values for convulsions. In general, this comparison (in Chapter 2, Section 2.1) indicated that reference values derived from mortality data would be similar to the overall RfD for RDX based on convulsions, assuming the application of the same extrapolation procedures and uncertainty factors.

The critical effect upon which the overall RfD is based (convulsions) is considered to be of high severity. Accordingly, EPA used a benchmark response (BMR) of 1% extra risk, consistent with the EPA's Benchmark Dose Technical Guidance. EPA presents uncertainties associated with the use of a 1% BMR in Section 2.1 of the Toxicological Review, along with the PODs one would derive using BMRs of 5 and 10% in the BMD modeling appendix of the Supplemental Information (Appendix D.1).

The IRIS program would like to encourage further public discussion of the relationship between convulsions and mortality, specifically, the impact of dose and duration of exposure on their occurrence, and other scientific input that could inform the selection of the BMR for convulsions.

With this science topic in mind, the sections of the toxicological review that would be relevant for you to review are:

-- Section 1.2.1, Nervous System Effects (pp. 1-4 to 1-21)
    -- This section references Appendix C, Section C.2, Human Studies, which summaries case reports of humans exposed acutely to RDX. This appendix can be found in the Supplemental Information volume.
-- Section 1.3.1, Effects Other than Cancer (pp. 1-69 to 1-72)
-- Section 2.1.1, Identification of Studies for Dose-Response Analysis of Selected Effects (pp. 2-2 to 2-4)
-- Section 2.1.2, Methods of Analysis (in particular p. 2-6, although other text related to human extrapolation may be useful)
-- Section 2.1.4, Derivation of Organ/System-Specific Reference Doses (pp. 2-16 to 2-17)
-- Section 2.1.5, Selection of the Overall Reference Dose (pp. 2-17 to 2-18)
-- Section 2.1.6, Comparison with Mortality LD_{01}s (pp. 2-18 to 2-21)
    -- This section references Appendix C, Section C.3.1, Mortality in Animals, which summaries evidence of reduced survival in animals exposed to RDX. This appendix can be found in the Supplemental Information volume.
-- Section 2.1.7, Uncertainties in the Derivation of the Reference Dose (p. 2-22)

Please don't hesitate to ask us if you have any questions. You mentioned that you might be calling in to our other preliminary conference call tomorrow afternoon.

Best wishes,

Vicki Soto

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